

## Evaluation of blood flow velocity to determine the effect of fortifiers on intestinal hemodynamics

Human milk fortifiers and intestinal hemodynamics

Nuriye Emiroğlu, Hüseyin Altunhan  
Department of Neonatology, Necmettin Erbakan University, Konya, Turkey

### Abstract

**Aim:** This study aimed to evaluate the effects of human milk fortifier (HMF) formulas on feeding intolerance and intestinal hemodynamics using superior mesenteric artery blood flow velocity (SMA-BFV).

**Material and Method:** The study was conducted on 36 infants born at a gestational age ranging from 26 to 326 weeks. Doppler-ultrasound (USG) was used to measure SMA-BFV. Demographic characteristics, the amount of gastric residue, and the number of stool passages were recorded for each of the patients in this study.

**Results:** The superior mesenteric artery peak systolic velocity (SMA-PSV) increment after HMF was statistically significant ( $P=0.0011$ ). A statistically significant increase was found in the amount of gastric residue and a significant decrease was found in the number of stool passages after the addition of HMF ( $p=0.0001$  and  $p=0.034$ , respectively).

**Discussion:** The use of HMF to achieve appropriate feeding and growth in preterm infants leads to an increase in SMA-BFV, a reduction in the number of stool passages, and an increase in the amount of gastric residue. It does not adversely affect intestinal hemodynamics.

### Keywords

Newborn; Human milk; Fortifiers; Mesenteric artery; Blood flow; Velocity

DOI: 10.4328/ACAM.20160 Received: 2020-03-12 Accepted: 2020-04-09 Published Online: 2020-04-19 Printed: 2020-11-01 Ann Clin Anal Med 2020;11(6):616-619  
Corresponding Author: Nuriye Emiroğlu, Department of Neonatology, Necmettin Erbakan University, 42080, Konya, Turkey  
E-mail: nuriyetarakci@hotmail.com P: +90 3322236000 F: +903322236182  
Corresponding Author ORCID ID: <https://orcid.org/0000-0003-2444-4725>

## Introduction

The gastrointestinal system of very low birth weight (VLBW) infants is not structurally and functionally mature. Human milk is very beneficial to preterm babies; therefore, it is the preferred way of feeding especially for VLBW infants. However, the amount of protein and other nutrients provided by human milk is not sufficient to meet the needs of VLBW infants [1]. Human milk fortifier (HMF) formulas have been proven to be safe and beneficial to provide intrauterine growth and nutritional support [2-4]. Thus, HMF is extensively recommended for feeding preterm infants. Furthermore, HMF supports the caloric increment and osmolarity of food. This may delay gastric emptying [5] and influence the amount of food passing through the intestinal system. The superior mesenteric artery (SMA) is the major source of blood flow in the small intestines and a portion of the large intestine. After birth, SMA blood flow velocity (SMA-BFV) increases to provide intestinal growth and oxygenation. In studies investigating the effect of HMF supplementation on feeding intolerance, different outcomes have been reported [5-7]. The present study used SMA-BFV to evaluate the effects of HMF on feeding intolerance and measure its effect on intestinal hemodynamics.

## Material and Methods

### Study Design

The hypothesis was tested using a crossover design. The study was conducted on 48 preterm infants born in the neonatal intensive care unit of Necmettin Erbakan University Hospital, with a gestational age ranging from 26 to 326 weeks that were fed with HMF formula. Preterm neonates were excluded from the study if they had a history of perinatal asphyxia, congenital anomalies, early-onset sepsis (culture-proven sepsis), suspected or proven necrotizing enterocolitis (NEC), or hemodynamically-significant patent ductus arteriosus (PDA), were fed formula during measurement while also being breastfed, and were administered vasoactive medications other than caffeine. Moreover, preterm infants with abnormal umbilical artery Doppler and/or birth weights below the third percentile were excluded. The study was approved by the Ethics Committee of Necmettin Erbakan University Faculty of Medicine. Informed written consent was obtained from at least one of the infants' parents.

### Feeding Protocol

Feeding was initiated for all infants with no contraindication for enteral feeding on the 1st and 2nd days. The protocol concerning time to initiate feeding, the feeding method (orogastric feeding), the increase in the feeding volume, the evaluation of feeding tolerance, and the collection and storage of human milk were the same for all of the infants in this study. All the infants were breastfed with their own mothers' human milk; a 24-hour supply of breast milk was provided daily and divided into amounts for feeding with 3-hour intervals each day. The breast milk was stored at a temperature under 4°C until used. Human milk intake was increased by 20 ml/kg/day. Feedings were given via nasogastric feeding tubes. When an enteral volume of 100 ml/kg/day was achieved, Eoprotin (Milupa, Friedrichsdorf, Germany) was added. Eoprotin was adjusted so that 4.4 gr was added to each 100 ml of human

milk. Gastric content was checked at every feeding. Gastric residue was defined as the return of 50% of the volume of milk given 3 hours before.

### Outcome Measures

SMA-BFV was measured after four consecutive feeding cycles 24 hours before and 24 hours after initiation of HMF. The measurements were performed at least 2 hours after feeding. SMA-BFV was measured using pulsed Doppler ultrasound (2004 PhilipsEnVisor C HD M2540A Ultrasound System). The flow was obtained by placing the Doppler sign 3 mm from the SMA originating from the aorta. Five consecutive constant waveforms were obtained, and a curve was observed. The SMA peak systolic velocity (PSV), end diastolic velocity (EDV), and Pourcelot's resistance index (RI)  $(PSV - EDV)/PSV$  were measured. All measurements were performed by the same neonatologist. The mean blood pressure of the infants, before and after initiation of HMF, was recorded. The amount of gastric residue and the number of stool passages 2 days before and 1 day after initiation of HMF were recorded. The infants' birth weights, gestational ages, genders, 5-minute APGAR scores, and time to initiation of HMF were recorded.

### Data Analysis

As descriptive statistics, mean  $\pm$  standard deviation was given for the continuous variables, and count and % were given for the categorical variables. The infants' blood flow velocity and blood pressure were compared using a paired student t-test. Stool passage and gastric residue were compared using the Poisson regression method. The Spearman's rank correlation coefficient was performed to determine the correlation among the numerical variables.  $P < 0.05$  was considered to be statistically significant. Statistical analysis was performed using SAS University Edition 9.4 software.

## Results

Forty-eight preterm infants were initially included in the study (Figure 1). The demographic and clinical characteristics and laboratory data of the studied neonates are listed in Table 1. None of the infants required administration of inotropes during the study period. Because eight infants had been fed breastmilk and formula, one of those infants needed nasal continuous positive airway pressure (NCPAP) and the measurements of three other infants could not be performed. Thus, their data were not included in the analysis. Consequently, a total of 36 preterm infants were included in the study.

The mean stool passage, gastric residue, and mean blood pressure values were obtained 24 hours before initiation of HMF and 24 hours after initiation of HMF. The results are presented in Table 2. A statistically significant increase was found in the mean blood pressure and the amount of gastric residue after the addition of HMF ( $p=0.0047$  and  $p=0.0001$ , respectively). A statistically significant decrease was found in the amount of stool passage after addition of HMF ( $p=0.034$ ) (Table 2).

Effect of HMF on SMA-BFV was represented in Table 3. Mean SMA-PSV at last 24 hours before initiation of HMF and at first 24 hours after initiation of HMF were  $0.39 \pm 0.14$  (cm/s) and  $0.5 \pm 0.19$  (cm/s), respectively; SMA-EDV were  $0.14 \pm 0.019$  (cm/s) and  $0.13 \pm 0.05$  (cm/s), respectively; and SMA-RI were  $0.67 \pm 0.10$  and  $0.74 \pm 0.08$ , respectively.

Table 1. Characteristics of the studied patients

N= 36	Mean ± SD
Gestational age (weeks)	29.6 ± 2.2
Birth weight (g)	1321 ± 362.5
Apgar 5 min	8 (7-9)
Gender n(%)	
Male	23 (63.9)
Female	13 (36.1)
Type of delivery n(%)	
C.S	28 (77.8)
Vaginal	8 (22.2)
Hb at time initiation of HMF	12.8 ±3.5
Time to initiation of HMF (days)	12.6 ± 6.1
Weight at time initiation of HMF (g)	1490 ± 386

C.S: caesarean; HB: haemoglobin, HMF: fortification of human milk SD: standard deviation

Table 2. Effect of HMFs on mean blood pressure, gastric residue and stool passage

	Before HMF Mean ± SD	After HMF Mean ± SD	95% CL Mean	p
Mean blood pressure	36.0 ± 7.78	41.9 ± 8.88	-9.8823 -1.9463	0.0047
Gastric residue	0.31 ± 0.71	1.28 ± 1.19		0.0001
Stool passage	2.94 ± 1.64	2.06 ± 1.48		0.034

Table 3. Effects of HMFs on SMA blood flow velocity

SMA-BFV	Before HMF Mean ± SD	After HMF Mean ± SD	95% CL Mean	p
PSV	0.39 ± 0.14	0.51 ± 0.19	-0.1896 -0.521	0.0011
EDV	0.14 ± 0.019	0.13 ± 0.05	-0.0254 0.0479	0.5372
RI	0.67 ± 0.10	0.74 ± 0.08	-0.1075 -0.0274	0.0016

SMA-BFV: Superior mesenteric artery blood flow velocity, HMF: Fortification of human milk, PSV: Peak systolic velocity EDV: End diastolic velocity RI: Resistance index

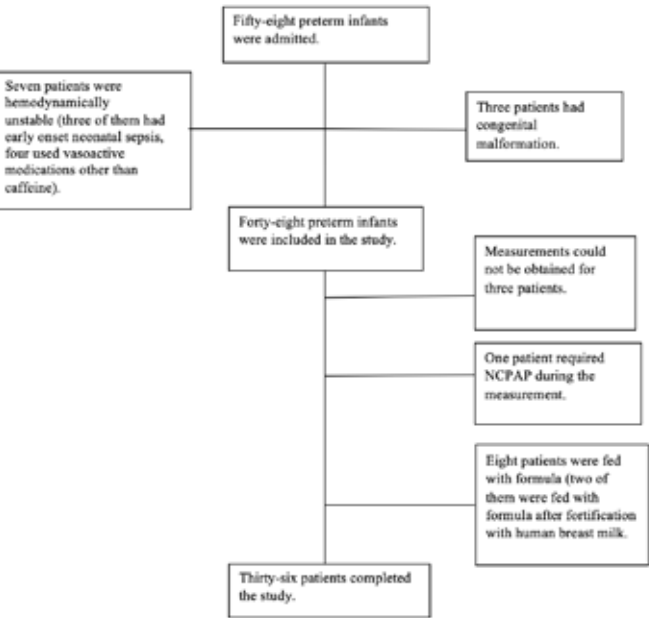


Figure 1. Algorithm of the preterm infants included in the study

The SMA-PSV, and SMA-RI with addition of HMF were higher compared to those fed only breast milk (p= 0.0011, p= 0. 0016); its effect on PSV-EDV was not significant (p= 0.5372).

Discussion

This study found that the addition of HMF increased SMA-BFV in preterm infants. This finding is significant because this study is a blind cross-over study and each of the preterm infants was evaluated; moreover, only one variable was used. The enteral feeding method and feeding volume may influence splanchnic blood flow in preterm infants. Fang et al. reported that there was a significant correlation between early toleration of enteral feeding and feeding increment in SMA-BFV and a reduction in SMA-RI [8]. Furthermore, they determined that an increase in the concentration of the plasma peptides as a result of being fed breast milk reduced vascular resistance and increased intestinal vasodilation and intestinal blood flow velocity [9]. In previous studies, SMA-BFV was shown to increase after feeding in preterm infants [8, 10-13]. In our study, SMA-BFV increased more in the preterm infants that were fed breast milk and HMF in comparison to those that were only fed breast milk.

Previous studies have reported different results regarding the correlation between enteral feeding volume and intestinal blood flow velocity [7,14,15]. Yanowitz et al. [13] found no correlation between enteral feeding volume and SMA blood flow. Maruyama et al. [15] reported a significant correlation between the amount of food that was increased in postnatal 4th and 6th days and time-averaged mean blood-flow velocity. In our study, we did not plan to show the relationship between feeding volume and SMA-BFV; however, we observed an indirect correlation between feeding volume and SMA-BFV. Specifically, in our study, administration of HMF led to an increase in the amount of gastric residue. This resulted in a reduction in the amount of food passing to the intestinal system. The question of whether or not SMA-BFV increased with the addition of HMF is related to HMF or the amount of nutrients passed into the intestinal tract is a problem that still needs to be solved.

In clinical practice, the status of intestinal motility is evaluated by determining the amount of gastric residue. Slower gastric emptying is associated with gastric residue, which leads to less feeding. The presence of gastric residue indicates feeding intolerance, and it demonstrates that an infant cannot digest and absorb food [16]. Ramiz et al. [17] reported that stomach content was more effectively emptied when the feeding volume was increased by adding fluids and decreasing the osmolarity of a standard feeding product in comparison to a feeding product with high osmolarity. Similarly, our study found that increasing the osmolarity of the feeding product by adding a fortifier without changing the feeding volume increased the amount of gastric residue. However, Yigit et al. [16] reported that the addition of HMFs did not slow down gastric emptying. They evaluated gastric emptying by measuring the antral cross-sectional area using B mode USG. In our study, the addition of a fortifier increased the gastric residual, thus slowing down gastric emptying and decreasing stool passage. While our study used the same HMF that Yigit et al. used, we obtained different results. This difference may have resulted from the method used to evaluate gastric emptying.

In conclusion, although the use of HMF to achieve appropriate feeding and growth in preterm infants leads to an increase in the amount of gastric residue and the number of stool passages, it does not adversely affect intestinal hemodynamics. To the best of our knowledge, this is the first study to investigate the effect of HMF on intestinal hemodynamics. Additional studies on this issue are needed.

#### Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

#### Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

**Funding:** None

#### Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

#### References

1. Miller J, Makrides M, Gibson RA, McPhee AJ, Stanford TE, Morris S, et al. Effect of increasing protein content of human milk fortifier on growth in preterm infants born at <31 wk gestation: a randomized controlled trial. *Am J Clin Nutr.*2012; 95(3):648–55.
2. Zuppa AA, Giraldo P, Scapillati ME, Maggio L, Romagnoli C, Tortorolo G. Effects on growth, tolerability and biochemical parameters of two different human milk fortifiers in very low birth-weight newborns. *Pediatr Med Chir.* 2004;26(1):45–49.
3. Berseth CL, Van Aerde JE, Gross S, Stolz SI, Harris CL, Hansen JW. Growth, efficacy, and safety of feeding an iron-fortified human milk fortifier. *Pediatrics.* 2004;114:699–706.
4. Porcelli P, Schanler R, Greer F, Chan G, Gross S, Mehta N, et al. Growth in human milk-fed very low birth weight infants receiving a new human milk fortifier. *Ann Nutr Metab.* 2000; 44:2–10.
5. Gathwala G, Shaw C, Shaw P, Yadav S, Sen J. Human milk fortification and gastric emptying in the preterm neonate. *Int J Clin Pract.* 2008;62(7):1039–43.
6. McClure RJ, Newell SJ. Effect of fortifying breast milk on gastric emptying. *Arch Dis Child.* 1996;74:60–62.
7. Ewer AK, Yu VYH. Gastric emptying in preterm infants: the effect of breast milk fortifier. *Acta Paediatr.* 1996;85:1112–15.
8. Fang S, Kempley ST, Gamsu HR. Prediction of early tolerance to enteral feeding in preterm infants by measurement of superior mesenteric artery blood flow velocity. *Arch Dis Child Fetal Neonatal Ed.* 2001;85(1):F42–45.
9. Pezzati M, Dani C, Tronchin M, Filippi L, Rossi S, Rubaltelli FF. Prediction of early tolerance to enteral feeding by measurement of superior mesenteric artery blood flow velocity: appropriate- versus small-for-gestational-age preterm infants. *Acta Paediatr.* 2004; 93(6):797–802.
10. Carver JD, Saste M, Sosa R, Zaritt J, Kuchan M, Barness LA. The effects of dietary nucleotides on intestinal blood flow in preterm infants. *Pediatr Res.* 2002;52:425–9.
11. Leidig E. Doppler analysis of superior mesenteric artery blood flow in preterm infants. *Arch Dis Child.* 1989;64:476–80.
12. Martinussen M, Brubakk AM, Vik T, Yao AC. Mesenteric blood flow velocity and its relation to transitional circulatory adaptation in appropriate for gestational age preterm infants. *Pediatr Res.* 1996;39:275–280.
13. Yanowitz TD, Yao AC, Pettigrew KD, Werner JC, Oh W, Stonestreet BS. Postnatal hemodynamic changes in very-low-birthweight infants. *J Appl Physiol.* 1999;87:370–80.
14. Havranek T, Thompson Z, Carver JD. Factors that influence mesenteric artery blood flow velocity in newborn preterm infants. *J Perinatol.* 2006;26:493–7.
15. Maruyama K, Koizumi T, Tomomasa T, Morikawa A. Intestinal blood-flow velocity in uncomplicated preterm infants during the early neonatal period. *Pediatr Radiol.* 1999;29:472–7.
16. Yigit S, Akgoz A, Memisoglu A, Akata D, Ziegler EE. Breast milk fortification: effect on gastric emptying. *J Matern Fetal Neonatal Med.* 2008;21(11):843–6.
17. Ramirez A, Wong WW, Shulman RJ. Factors regulating gastric emptying in preterm infants. *J Pediatr* 2006;149:475–9.

#### How to cite this article:

Nuriye Emiroğlu, Hüseyin Altunhan . Evaluation of blood flow velocity to determine the effect of fortifiers on intestinal hemodynamics. *Ann Clin Anal Med* 2020;11(6):616–619